

COVID-19 Vaccine Side Effects and Long-Term Neutralizing Antibody Response

A Prospective Cohort Study

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Background: Concern about side effects is a common reason for SARS-CoV-2 vaccine hesitancy.

Objective: To determine whether short-term side effects of SARS-CoV-2 messenger RNA (mRNA) vaccination are associated with subsequent neutralizing antibody (nAB) response.

Design: Prospective cohort study.

Setting: San Francisco Bay Area.

Participants: Adults who had not been vaccinated against or exposed to SARS-CoV-2, who then received 2 doses of either BNT162b2 or mRNA-1273.

Measurements: Serum nAB titer at 1 month and 6 months after the second vaccine dose. Daily symptom surveys and objective biometric measurements at each dose.

Results: 363 participants were included in symptom-related analyses (65.6% female; mean age, 52.4 years [SD, 11.9]), and 147 were included in biometric-related analyses (66.0% female; mean age, 58.8 years [SD, 5.3]). Chills, tiredness, feeling unwell, and headache after the second dose were each associated with 1.4 to 1.6 fold higher nAB at 1 and 6 months after vaccination. Symptom count and vaccination-induced change in skin temperature

and heart rate were all positively associated with nAB across both follow-up time points. Each 1 °C increase in skin temperature after dose 2 was associated with 1.8 fold higher nAB 1 month later and 3.1 fold higher nAB 6 months later.

Limitations: The study was conducted in 2021 in people receiving the primary vaccine series, making generalizability to people with prior SARS-CoV-2 vaccination or exposure unclear. Whether the observed associations would also apply for neutralizing activity against non-ancestral SARS-CoV-2 strains is also unknown.

Conclusion: Convergent self-report and objective biometric findings indicate that short-term systemic side effects of SARS-CoV-2 mRNA vaccination are associated with greater long-lasting nAB responses. This may be relevant in addressing negative attitudes toward vaccine side effects, which are a barrier to vaccine uptake.

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Vaccination against SARS-CoV-2 has been repeatedly shown to reduce infections, hospitalizations, and mortality, but protection wanes considerably over time for all of these outcomes, even after booster vaccination (1). Moreover, uptake of booster vaccinations has been low, with only 17% of the U.S. population having received the bivalent booster as of May 2023, despite wide vaccine availability for more than 6 months at that time (2). Among people who received at least 1 dose of a COVID-19 vaccine, the most commonly reported reasons for not having received a booster were: first, a perception of low added benefit in protection from illness, given a personal history of prior vaccination or SARS-CoV-2 infection and, second, worry about side effects (3, 4).

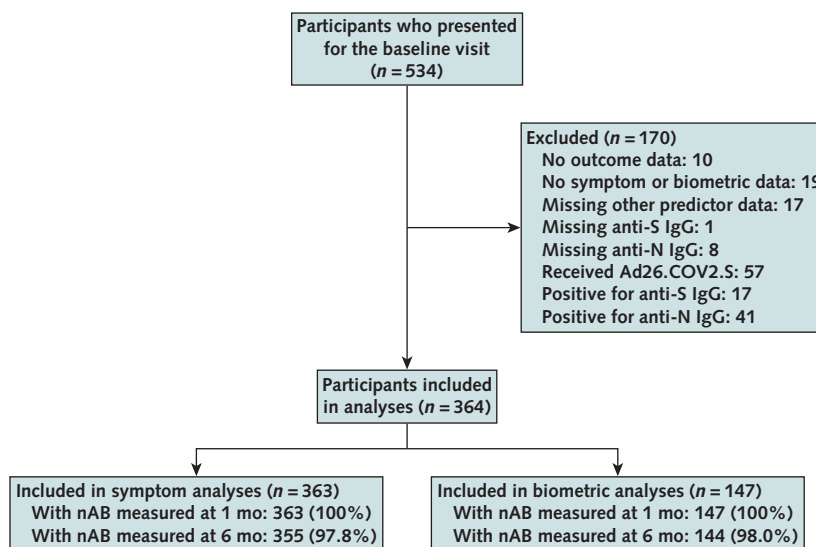
Recent evidence has suggested that greater systemic symptoms after SARS-CoV-2 vaccination may reflect a more potent immune response (5-7). A deeper understanding of this relationship may help to

address low rates of vaccine uptake. Specifically, public health messaging might aid uptake by reframing short-term postvaccination symptoms as positive indications that the vaccine is likely to be working rather than as undesirable side effects (8, 9).

Although there are several reports suggesting that SARS-CoV-2 vaccine reactogenicity (that is, resulting symptom burden or physiologic perturbation) predicts a higher subsequent anti-spike immunoglobulin level (5-7), only a few studies have specifically measured neutralizing antibodies (nABs) (10-12). Results from these studies are inconsistent, and they have only measured short-term nAB responses. Quantifying functional

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Figure 1. Flow chart of participants and observations.

anti-N IgG = anti-nucleocapsid immunoglobulin G; anti-S IgG = anti-spike immunoglobulin G; nAB = neutralizing antibody.

antibody activity (that is, nAB) is important because, although they are correlated, the effects of SARS-CoV-2 vaccines on nAB and absolute anti-spike immunoglobulin G (IgG) are dissociable, and nABs specifically seem critical in conferring protection from COVID-19 (13, 14). Only approximately 50% of the variability in nABs is predictable from anti-spike IgG (13), and nABs have been reported to have a larger effect size (that is, lower hazard ratio per 10-fold increase) than anti-spike IgG in predicting subsequent COVID-19 incidence (14). It has been demonstrated that providing animals with nABs alone confers protection against disease even after high-dose SARS-CoV-2 exposure (15), and, in 1 study in humans, the nAB level was estimated to mediate more than two thirds of vaccine efficacy (14). A recent meta-analysis (16) and a large pooled cohort analysis (17) of vaccination studies have estimated the correlation between average vaccine-evoked nABs and vaccine efficacy to be 0.81 and 0.91, respectively.

We used convergent self-reported symptom and objective biometric measurements to identify predictors of subsequent serum nAB concentration at 1 and 6 months postvaccination in a cohort of adults who received the initial 2-dose series of BNT126b2 or mRNA-1273. Self-reported variables included the presence or absence of 13 individual symptoms and total systemic symptom count. Biometric variables included measures of vaccination-induced change in skin temperature (ST), heart rate (HR), heart rate variability (HRV), and respiratory rate (RR).

METHODS

Participants

Persons included in analyses were participants in the Building Optimal Antibodies Study (18), a large,

single-site, observational study designed to identify psychosocial, behavioral, and biological predictors of immune responses to COVID-19 vaccination. Participants were adults aged 18 years and older who did not report having any immune-related disease (that is, autoimmune conditions, viral hepatitis, or HIV) or active cancer and were not taking medications known to impact the immune system (for example, immunomodulators or steroids). Participants were recruited via e-mail newsletters to patients and staff at the University of California, San Francisco, and via social and traditional media. Ethical approval was provided by the Institutional Review Board at the University of California, San Francisco, and all study participants provided written informed consent. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting checklist for cohort studies is provided in **Supplement Table 1** (available at [Annals.org](#)).

Serum was collected from study participants before they received a COVID-19 vaccine and again 1 month and 6 months after they completed their initial 2-dose series of BNT126b2 or mRNA-1273. Participants independently arranged to be vaccinated in the community, and vaccination date and type were later determined using official records. History of SARS-CoV-2 infection was examined by measuring levels of anti-spike IgG antibodies at baseline and anti-nucleocapsid IgG antibodies at 6 months. Participants with a positive result on either test were excluded from analyses. Recipients of Ad26.COV2.S were excluded from analyses given that use of this vaccine is no longer authorized by the U.S. Food and Drug Administration. Other reasons for exclusion of

Table. Sample Characteristics of the Study Population

Characteristic	Symptom Analyses (n = 363)	Biometric Analyses (n = 147)*
Mean age (SD), y	52.4 (11.9)	58.8 (5.3)
Mean body mass index (SD)	26.9 (5.9)	27.4 (6.4)
Female, n (%)	238 (65.6)	97 (66.0)
Vaccine type: BNT162b2, n (%)	235 (64.7)	94 (63.9)
Smoked at baseline, n (%)	6 (1.7)	3 (2.0)
Race and ethnicity, n (%)		
Asian	84 (23.1)	26 (17.7)
Black/African American	6 (1.7)	4 (2.7)
Hispanic/Latinx	33 (9.1)	7 (4.8)
Other/multiracial/unknown	27 (7.4)	7 (4.8)
White	213 (58.7)	103 (70.1)
Education level, n (%)		
4-y degree	129 (35.5)	51 (34.7)
Professional degree or doctorate	178 (49.0)	76 (51.7)
Some college or less	56 (15.4)	20 (13.6)
Household income, n (%)		
Less than \$50 000	37 (10.2)	17 (11.6)
\$50 000 to less than \$100 000	69 (19.0)	28 (19.0)
\$100 000 to less than \$200 000	108 (29.8)	48 (32.7)
\$200 000 or more	94 (25.9)	35 (23.8)
Prefer not to answer	55 (15.2)	19 (12.9)
Marital status, n (%)		
Married or with a long-term partner	213 (58.7)	91 (61.9)
Never married	108 (29.8)	36 (24.5)
Divorced or separated	35 (9.6)	16 (10.9)
Widowed	7 (1.9)	4 (2.7)

* Biometric wearable devices were provided to a subset of participants who had a compatible smartphone and were almost exclusively (99%) older than age 50 years.

participants from analyses are provided in the flow chart in Figure 1.

Outcome

The nABs against SARS-CoV-2 were measured via pseudovirus assay at 1 month and 6 months after vaccination as described previously (18). In brief, serum from each participant was serially diluted and incubated with pseudovirus expressing full-length SARS-CoV-2 protein (Wuhan/D614G strain), permitting virion binding and neutralization by host antibodies. Serum-virus mixtures were then incubated with susceptible cells, which allowed the remaining functional pseudovirus to deliver a luciferase reporter gene intracellularly. After 66 to 72 hours, the medium was removed, lysis buffer and luciferase substrate were added, and luciferase activity was measured as luminescence. The nAB titers were expressed as the inhibitory dose 50 (ID50), defined as the serum dilution corresponding to a reduction of relative light units by 50% compared with serum-free control wells.

Daily Symptom Surveys

Participants were sent links to a survey each evening for 6 days, beginning on the date they anticipated receiving each dose of a SARS-CoV-2 vaccine. The survey included the question, “Did you experience any of the following physical symptoms today? (Check all that apply).” The following options were

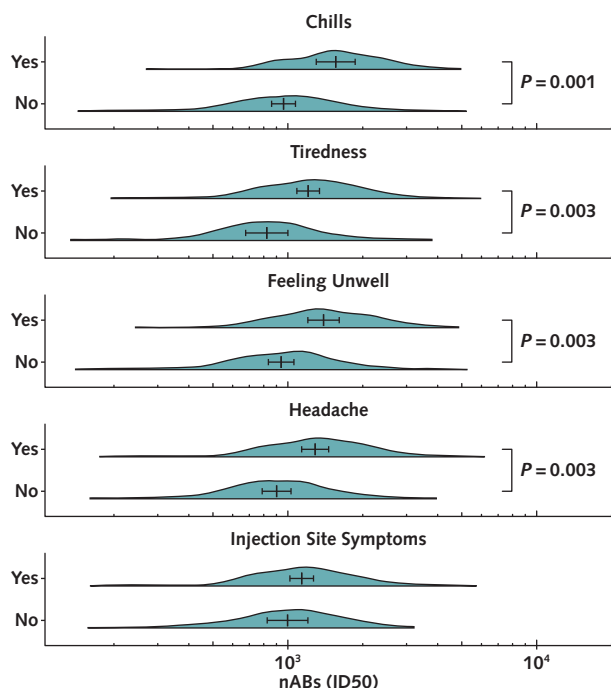
provided: tiredness; headache; muscle pain; chills; joint pain; fever; nausea/vomiting; feeling unwell; tender or swollen lymph nodes (lymphadenopathy); injection site pain, redness, or swelling; pain or swelling in the arm that did not get the vaccination; other allergic reactions (difficulty breathing, swelling of face/throat, rash); stomachache. For each survey entry, vaccine dose dates were used to calculate calendar days since receipt of either dose 1 or 2. At each vaccine dose, for each symptom and participant, data were collapsed to reflect either symptom presence in at least 1 survey entry or symptom absence in all available survey entries. The median number of survey entries received per participant was 5 (IQR, 4 to 6) for both dose 1 and 2, with the maximum possible being 6. As an index of systemic symptom burden, a symptom count variable was created by calculating the number of distinct symptoms each participant reported, excluding injection site symptoms.

Biometric Collection and Analysis

The HR, HRV, RR, and ST data were collected from a subset of participants using a biometric wearable device, the Oura Ring (Oura Health Oy). Except for 1, all participants who provided biometric data were older than age 50 years because only these participants were actively offered devices.

During sleep, HR and HRV were recorded in 5-minute intervals whereas ST was recorded in 1-minute intervals. The RR was only available as a nightly average. To test the hypotheses that short-term effects of vaccination on nighttime HR, HRV, ST, and RR are predictive of subsequent nAB response, it was necessary to first derive a single summary value of vaccination-induced change in each physiologic domain for each participant. For this purpose, for each domain, we used a multistep procedure to identify the summarization approach with the best statistical evidence of vaccination-induced change (19, 20); see the **Supplement Methods** (available at Annals.org) for details. Ultimately, each nightly time series of observations was first summarized into single nightly values for each participant by taking the nightly 99th percentile (that is, the “stable maximum”) for ST and HRV and by taking the nightly 1st percentile (that is, the “stable minimum”) for HR. Then, for each participant, for each physiologic domain, the values on the first and second night after vaccination were each subtracted from a participant-specific norm. Finally, the greater of the 2 deviations from the participant norm (that is, the vaccination-induced change on either the first or second night after vaccination) was taken as each participant’s single value of vaccination-induced change. Descriptive and test statistics for candidate summary variables of vaccination-induced change are provided in **Supplement Table 2** (available at Annals.org). Spearman correlations between final summary variables

Figure 2. Association between symptoms after the second vaccine dose and subsequent nAB levels.



Each of 13 symptoms after each vaccine dose was individually tested as a predictor of nAB levels at 1 month and 6 months later in multivariable mixed-effects models. The nAB titer was expressed as the ID50. After correcting for multiple comparisons, 4 symptoms remained statistically significant predictors of nABs, all only when measured at dose 2: chills, tiredness, feeling unwell, and headache. Injection site symptoms are included in the figure for comparison. Density plots are provided, and vertical bars represent the marginal means \pm 95% CIs. No interaction terms between a symptom and vaccine or outcome time point were statistically significant; therefore, presented marginal means represent the average effect across both vaccines and both outcome time points. ID50 = inhibitory dose 50; nAB = neutralizing antibody.

and symptom count are presented in the Supplement Figure (available at [Annals.org](https://annals.org)).

Statistical Analysis

All data analysis was performed in R (version 4.2.2). For all analyses, mixed-effects models were fit to nAB data collected at 1 month and 6 months after completion of the second vaccine dose. All models included a core set of terms, including main effects of vaccine (that is, BNT-162b2 vs. mRNA-1273), time point, sex, age, baseline smoking status, and body mass index, and a time point \times vaccine interaction. The statistical significance of these terms has been previously described (18). Here, for each vaccine dose, 18 variables were examined as predictors of subsequent nAB level: the presence or absence of 13 symptoms, the total count of reported symptoms (excluding injection site symptoms), and the levels of 4 biometric measurements. For each variable, a model was created by adding to the core model structure the

following terms: a main effect, an interaction with vaccine, an interaction with time point, and the 3-way interaction between these variables. Thus, 4 hypotheses of interest were tested in each model, except where interaction terms were removed to resolve multicollinearity (see the Supplement Methods for more detail). Predictor significance was tested using F statistics. Ultimately, 126 *P* values (1 to 4 per model) were drawn from 36 models; these were consolidated and corrected for multiple comparisons using the adaptive Benjamini-Hochberg method with a false discovery rate threshold of 0.05 (21, 22). Statistical significance was defined as corrected *P* < 0.05; significant F statistics were followed by post hoc *t* tests without further correction. All presented results represent marginal effects, that is, effects adjusted for the other terms in the model. Thus, where results are presented without respect to outcome time point, these represent average effects across both time points. For statistically significant continuous predictors, the partial correlation (r_p) was provided alongside absolute effect sizes. Visualizations represent marginal means (that is, least-squares means) \pm 95% CIs along with partial residuals. Detailed information can be found in the Supplement Methods.

Role of the Funding Source

Neither the National Institutes of Health nor Oura Health Oy had any role in the design or conduct of the study; the collection, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

RESULTS

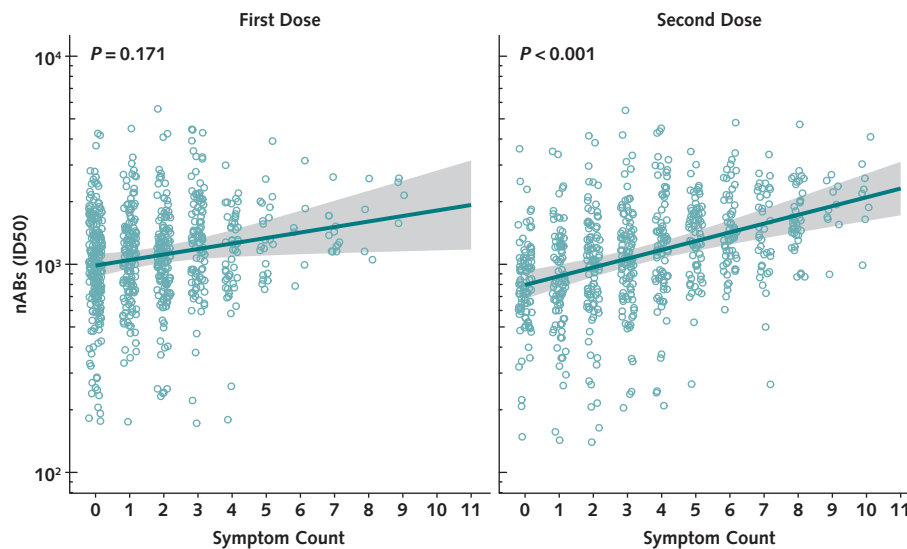
Sample Characteristics

A total of 534 people were recruited for the broader study, of whom 364 met criteria for inclusion in the present analyses (Figure 1). Of these, symptom data were collected from 363 participants, and biometric data were collected from 174 participants. Sample characteristics are provided in the Table.

Symptom Predictors of Neutralizing Antibodies

The frequency of each symptom at each vaccine dose is provided in Supplement Table 3 (available at [Annals.org](https://annals.org)). Among participants who reported at least 1 symptom after dose 1, 91.5% also reported at least 1 symptom at dose 2. Among participants who reported no symptoms after dose 1, 74.1% reported at least 1 symptom at dose 2. Test statistics and multiplicity-corrected *P* values for all symptom and biometric analyses are provided in Supplement Table 4 (available at [Annals.org](https://annals.org)). An example of a full model is provided in Supplement Table 5 (available at [Annals.org](https://annals.org)).

Figure 3. Association between symptom count following each vaccine dose and subsequent nAB levels.



Symptom count was intended as a measure of systemic symptom burden, so injection site symptoms were excluded from counting. Symptom count after the second dose was a statistically significant predictor of subsequent nAB level ($P < 0.001$). For both doses, there was no statistically significant interaction between symptom count and vaccine or outcome time point (1 month and 6 months after the second dose); therefore, results represent the average relationship across both time points and both vaccines (that is, marginal means \pm 95% CIs). Each open circle represents the partial residual for 1 observation. ID50 = inhibitory dose 50; nAB = neutralizing antibody.

After correction for multiple comparisons, no statistically significant associations were identified between the presence or absence of any symptom at dose 1 and subsequent nABs. For dose 2, main effects were significant for 4 of 13 symptoms (Figure 2). Specifically, nABs were higher for participants reporting versus not reporting the following symptoms at dose 2: chills (1.62 fold higher ID50 [95% CI, 1.31 to 2.01]), feeling unwell (1.48 fold higher ID50 [CI, 1.22 to 1.79]), tiredness (1.47 fold higher ID50 [CI, 1.17 to 1.83]), and headache (1.43 fold higher ID50 [CI, 1.19 to 1.72]). Because symptom presence did not interact with outcome time point or vaccine for any symptom, presented values represent the average association across both vaccines and both outcome time points.

Symptom Count as a Predictor of Neutralizing Antibodies

For dose 1, there were no main or interaction effects involving symptom count. For dose 2, no interactions were significant, but there was a main effect of symptom count (Figure 3), involving a 1.10 fold higher ID50 per additional symptom (CI, 1.06 to 1.14; $r_p = 0.27$ [CI, 0.17 to 0.36]).

Biometric Predictors of Neutralizing Antibodies

For vaccination-induced change in nightly 99th-percentile ST at dose 1, there were no significant main or interaction effects. However, at dose 2, there was a significant interaction between outcome time point and vaccination-induced change in nightly 99th-percentile

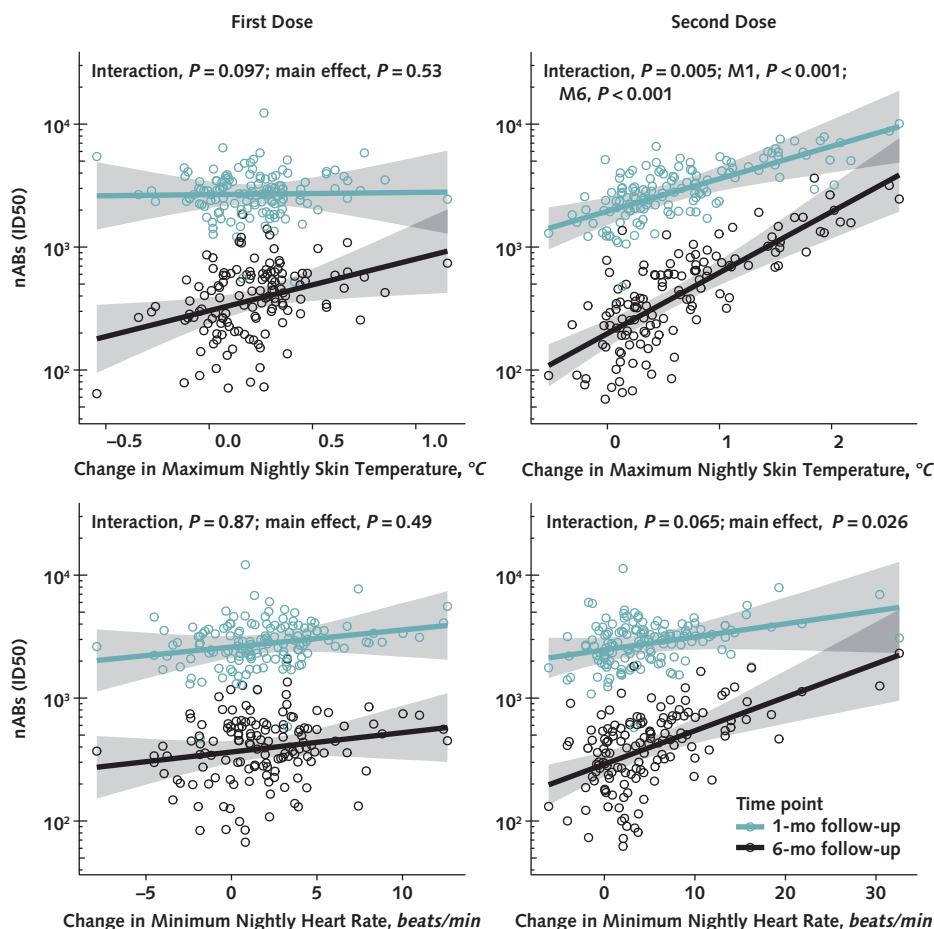
ST (Figure 4, top right). Post hoc testing revealed that vaccination-induced change in ST at dose 2 was predictive of nAB at 1-month follow-up (fold change in ID50 per $^{\circ}\text{C}$, 1.84 [CI, 1.33 to 2.53], $P < 0.001$; $r_p = 0.27$ [CI, 0.13 to 0.39]) and at 6-month follow-up (fold change in ID50 per $^{\circ}\text{C}$, 3.13 [CI, 2.26 to 4.33], $P < 0.001$; $r_p = 0.45$ [CI, 0.33 to 0.55]), with the larger effect size at the 6-month follow-up being responsible for the interaction.

For vaccination-induced change in nightly 1st-percentile HR at dose 1, there were no significant main or interaction effects. However, at dose 2, a significant main effect of vaccination-induced change in nightly 1st-percentile HR was observed (Figure 4, bottom right), in the absence of any interaction with outcome time point or vaccine. For each 10 beat per minute increase in HR at dose 2 from a participant's norm, ID50 increased by 1.54 fold (CI, 1.18 to 2.02; $r_p = 0.27$ [CI, 0.10 to 0.41]) on average across both outcome time points.

Neither vaccination-induced change in nightly 99th-percentile HRV nor in average nightly RR was significantly predictive of subsequent nAB via either main or interaction effects, for either vaccine dose.

DISCUSSION

We show here that people who reported experiencing chills, tiredness, feeling unwell, or headache after the second dose of a SARS-CoV-2 vaccine subsequently had 1.4 to 1.6 times the nAB level of people who did not report each symptom, at 1 month and

Figure 4. Association between vaccination-induced change in 2 physiologic domains and subsequent nAB levels.

A subset of study participants wore biometric devices that collected physiologic measurements during sleep. Graphs depict the relationship between vaccination-induced change in nightly maximum (99th percentile) skin temperature (top row) and nightly minimum (1st percentile) heart rate (bottom row) and subsequent nAB level at each outcome time point. Vaccination-induced change in maximum skin temperature at dose 2 predicted nAB level at both outcome time points, with a stronger association for the 6-month (M6) than the 1-month (M1) outcome (top right). There was a main effect of vaccination-induced change in minimum heart rate on subsequent nAB level (bottom right). Each open circle represents the partial residual for 1 observation. ID50 = inhibitory dose 50; nAB = neutralizing antibody.

6 months later. We also show that each additional symptom experienced after dose 2 predicted a 1.1-fold increase in subsequent nABs. This means that, on average, participants reporting 7 total symptoms subsequently had roughly double the nAB level of participants reporting 0 symptoms. Using objective biometric data, we present convergent findings showing that greater vaccination-induced change in ST and HR, specifically at dose 2, predicts greater nAB at both 1 month and 6 months later. Effect sizes were again large; for example, every 1 °C of vaccination-induced ST change was associated with a tripling of the nAB level at 6 months later.

Several prior publications have examined the association between systemic symptoms after receipt of a SARS-CoV-2 messenger RNA (mRNA) vaccine and subsequent nAB level, with inconsistent results. In 1 report, none of 3 local or 8 systemic symptoms, nor the

presence of any local or any systemic symptom, predicted nAB 4 weeks later (10). By contrast, in other work, the presence of at least 1 systemic symptom was associated with higher nAB at 12 to 19 days after dose 2 (12) and at 54 days after dose 3 (11). There are a few other reports examining the association between reactivity to SARS-CoV-2 vaccination and subsequent nAB, but interpretability is limited due to low sample sizes (4 to 8 per condition) (23); the analysis only of nAB trajectories over time (24), which are confounded by absolute initial levels (13); and the use of a mixed sample of mRNA and adenoviral vector vaccine recipients (25).

There are several key strengths of our study compared with prior studies (10–12). First, neither of the previous 2 studies reporting a significant association between symptoms and nAB examined individual symptoms as predictors. Here, we show that chills,

tiredness (or fatigue), feeling unwell, and headache have the strongest predictive relationship with nABs. Second, these studies all measured nABs within 2 months of receipt of the second dose of an mRNA vaccine, whereas our report includes measurements at 6 months. This long follow-up is important given that after receiving the initial vaccine series, typically a minimum of several months pass before people receive a booster dose. Predictive relationships may differ for different outcome time points, and, indeed, in the present study, we observed a relationship between vaccination-induced change in ST and nAB that was a stronger predictor of the 6-month than the 1-month outcome. Third, in addition to self-report measures, which might be affected by between-participant differences in the tendency to notice, recall, and report side effects, we use objective biometric measurements of physiologic perturbation that are not vulnerable to these influences. Using this data, we present findings that align with our self-report data. Only 1 prior study has used non-self-report objective biometric data to predict subsequent humoral immune response after SARS-CoV-2 vaccination (26). That study found positive associations between vaccination-induced change in ST and HR and subsequent anti-spike immunoglobulin at roughly 1 month after vaccination in a mixed mRNA and adenoviral vector vaccine sample. Here, we extend those findings, demonstrating similar relationships for nABs and at 6 months in an mRNA vaccine sample. Finally, our study is among the first to examine associations between symptoms and nABs in a community sample rather than a convenience sample of health care workers.

There are several limitations to our study. First, our results are from people who received only the initial COVID-19 vaccine series. It is not clear whether the relationships observed here would apply to people undergoing initial vaccination or revaccination using updated vaccine formulations. Second, our results are from people who did not have any serologic evidence of SARS-CoV-2 infection. It is unclear whether people with a previous history of SARS-CoV-2 infection would exhibit the same predictive ability of symptoms and vaccination-induced changes in biometrics. However, among people receiving a 2-dose mRNA vaccination, those with a prior history of SARS-CoV-2 infection have been reported to have both greater subsequent anti-spike IgG concentrations (27) and greater reactogenicity (28), suggesting that a predictive association between reactogenicity and nABs is likely in previously infected people as well. A third limitation is that our pseudovirus assay used the spike protein from the original Wuhan/D614G strain of SARS-CoV-2, which may limit generalizability of the findings. Fourth, our biometric data were collected almost entirely from people older than age 50 years, limiting the generalizability of our biometric findings. Fifth, it should be noted that correction for multiple

comparisons affects only the *P* value, not the effect size. Thus, qualitative statements about significance or nonsignificance are adjusted for multiplicity, whereas quantitative estimates of effect sizes for statistically significant results may be biased upward. Finally, we only address humoral immunity in this study, and although evidence suggests that nABs mediate roughly two thirds of SARS-CoV-2 mRNA vaccine efficacy (14), cellular immunity is believed to play an important role in protection from severe disease (29, 30).

It should be noted that our results do not justify inferences about any given person's level of nABs or protection from SARS-CoV-2 infection. For example, although participants reporting tiredness had an average nAB level that was 1.5 times the level of those not reporting tiredness, not every person with tiredness had higher nABs than every person without tiredness. Therefore, tiredness should not be taken to mean something definitive about a given person's nAB level. Relatedly, although nAB level has been shown to have a strong relative association with risk for COVID-19, the relationship with absolute risk will be variable and dependent on base infection rates in any given population (14, 31).

In sum, we show in a community sample that systemic symptoms and increases in ST and HR after SARS-CoV-2 mRNA vaccination predicted a higher subsequent nAB level. We show that these relationships were stronger when predicting long-term rather than short-term nAB outcome. These data may help to address the low rate of ongoing vaccine uptake (8, 9), given that this seems to be at least partly the result of worry about side effects (4).

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Reproducible Research Statement: *Study protocol:* Not available. *Statistical code and Data set:* Available from the corresponding authors upon reasonable request.

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